RECEIVED
CENTRAL FAX CENTER

NOV 04 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial Number:	10/688,741
Application Filed:	04/26/2002
Applicant(s):	KREAM, Richard M.
Title:	Method of inhibiting opioid tolerance with chimeric hybrid analgesics
Group:	1600
Art Unit:	1647
Examiner:	Robert Landsman, Ph.D.

DECLARATION

I, Richard M. Kream, hereby submit this declaration pursuant to 37 CFR §1.132 and declare as follows:

1. The inventorship of the pending application is correct. My application discloses subject matter invented by me (the applicant) rather than derived from the patentee(s) of U.S. Patent 6,759,520 notwithstanding the inventorship of that patent.

2. Additionally, and without limiting the generality of the preceding paragraph, no one communicated to me a complete conception of my invention, much less something sufficient to enable one of ordinary skill in the art to construct and successfully operate the invention.

I declare under penalty of perjury that the foregoing is true and correct. Executed on November 2, 2006.

Richard M. Kream, Ph.D.

coworkers and Schiller provide specific indications for maintaining opioid activity following chemical modification of the multi-ringed non-peptide structures characteristic of morphinans, benzomorphans, and phenylpiperidines, as described for opioid peptide analogs. The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS.

In brief, the teachings of Portoghese and coworkers provide the following guidelines for preserving high affinity MOR activity for all non-peptide opioid domains found in the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other neuropeptide receptors, within the CNS. Their teachings indicate that the A ring OH group at position 3 must be conserved during synthesis and/or conjugation to active SP fragments, or for that matter any active fragment of any peptide possessing a pharmacologically distinct C-terminal activation domain, though a linker molecule. Consistent with the major body of published opioid research, conservation of the A ring OH group at position 3 is required for high affinity MOR activation. Thus, the A ring OH group at position 3 may be protected during synthesis or conjugation via covalent linkage to well recognized blocking groups that include Acetyl or T-butyl moieties. Following synthesis or construction of chimeric hybrid conjugates the Acetyl or T-butyl moieties are removed by gentle chemical treatment yielding non-peptide chemical moieties with a free A ring OH group at position 3.

The teachings of Portoghese and coworkers also indicate that the B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure is an appropriate site for chemical modification due to its location at a point distal to the obligate A ring OH group at position 3 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure. Chemical modification and linkage of the non-peptide opioid domain of molecules of the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other classes of neuropeptide receptors, within the CNS at a position spatially separated and distal to the obligate A ring OH group will permit binding in a sterically unhindered fashion to the mu opioid receptor. The B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure may be further oxidized to a keto group with full retention of opioid activity. OH and keto groups are generally employed as chemical moieties capable of covalently linking discrete chemical entities through ester or ether chemistry. Finally, the teachings of Portoghese and coworkers indicate that multiple positions of the B ring, including the OH group at position 6 of morphine, or an equivalent position on the morphinan or benzomorphan multi-ringed structure, may be

chemically modified without effecting opioid activity mediated by the obligate A ring OH group.

The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences, or for that matter any active fragment of any peptide possessing a pharmacologically distinct N-terminal activation domain, are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller, an authority in the design and synthesis of chemically modified opioid peptide sequences, and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of MORs and SPRs, or for that matter any other class of neuropeptide receptors, within the CNS.

Guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller, an authority in the design and synthesis of chemically modified opioid peptide sequences, are extended to cover the breadth of all active fragments of any peptide possessing a pharmacologically distinct N-terminal activation domain by the teachings of Shimizu and coworkers (6) and by the teachings of Jette and coworkers (7). Shimizu and coworkers teach that the intact N-terminal 14 amino acid fragment of the complete 34 amino acid sequence of parathyroid hormone (PTH) represents the pharmacologically distinct N-terminal activation domain for the PTH receptor (6). Limited substitution within the autonomous pharmacologically distinct N-terminal activation domain of PTH, designated PTH (1-14), by the un-natural amino acid alpha-aminoisobutyric acid dramatically enhances the capacity of PTH (1-14) to activate the PTH receptor by 2-4 orders of magnitude (6). In similar fashion, the teachings of Jette and coworkers indicate that the N-terminal 29 amino acid peptide fragment of the complete 44 amino acid peptide sequence of human Growth Hormone-releasing factor (hGRF) represents the pharmacologically distinct N-terminal activation domain for the hGRF receptor (7). The teachings of Jette and coworkers also provide enablement for increasing the biological activity of the N-terminal 29 amino acid peptide fragment of hGRF, designated hGRF(1-29), via the method of conjugation of hGRF(1-29) through amino acid 29 to an appropriate carrier protein protein (7).

The teachings of Shimizu and coworkers (6) and Jette and coworkers (7) indicate chemical modifications and strategically defined points of chemical conjugation, i.e., positions spatially separated and distal to the N-terminal, of autonomous distinct N-terminal activation domains represented by the peptide fragments PTH (1-14) and hGRF (1-28), respectively, will dramatically enhance biological activities. Because PTH (1-14) and hGRF (1-28) themselves mediate different, physiologically distinct, pharmacological activities, as well as different, physiologically distinct, pharmacological activities as established for morphine, morphine congeners, and N-terminal activation domains of opioid peptide fragments, guidelines provided by Portoghese and coworkers, in reference to the teachings of Liederer and coworkers and Schiller, are generalized and extended by